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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WILLIAMS, LEONARD M	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 08/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/049,327	MEYTHALER ET AL.	
	Examiner	Art Unit	
	Leonard M. Williams	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-7 and 29-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-7 and 29-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

Status of Claims

The remarks received in the office 6/1/2006 have been entered. No claims have been amended, cancelled or added.

Claims 1, 4-7 and 29-42 are pending.

Response to Arguments

Applicant's arguments filed 6/1/2006 have been fully considered but they are not persuasive.

The applicant's have asserted, on page 6 of the remarks, that there is no reasonable expectation of success and that a *prima facie* case of obviousness has not been established. The examiner respectfully disagrees.

The applicant's state on page 7 of the remarks: "Applicant submits that Grilli et al. provides evidence that pretreatment of cultured cells with a non-steroidal anti-inflammatory compound protects some cells from glutamate receptor mediated injury." The applicants further go on describing various in vitro methods and further aspects wherein Grilli et al. demonstrates the protection of cells from damage. The applicants further state on page 8 of the remarks: "As Applicant noted previously, the Grilli et al. specification only describes instances or pre-treatment of cells in order to protect the cells from glutamate receptor-mediated neuronal damage." Thus the applicant's seem to indicate that Grilli et al. is only directed toward "pre-treatment" and "prevention" of

neuronal cell damage. The examiner respectfully disagrees. Despite this it is clear from the title of Grilli et al.'s application that both prevention and treatment of neurodegenerative diseases are contemplated. On page 4 lines 6-9 of Grilli et al., it states: "Moreover, it has been proved [J. Rogers et al. Neurology 43, 1609, (1993)] that another NSAID reduces the progression of cognitive decline in AD patients." As this statement clearly indicates treatment of a pre-existing condition with NSAIDs, it is inappropriate to assume that Grilli et al. would be limited to only preventative measures and that only pre-treatment and prevention of neurodegeneration is contemplated. Further on page 5 lines 1-10, Grilli states: "...anti-inflammatory compounds of formula (I) and the pharmaceutically acceptable salts and metabolites thereof have properties making them suitable for the prevention and/or the treatment of glutamate receptor-mediated neuronal damages..." Again clearly Grilli et al. contemplates both prevention and treatment.

The applicants state on page 9 of the remarks: "Furthermore, even if Myseros et al. described administration of glutamate receptor antagonists having a therapeutic effect when administered following FPI, this would not ameliorate the lack of teaching in these references that administration of NSAIDS can be performed with therapeutic effect following the immediate release of excitotoxic neurotransmitters." The examiner respectfully disagrees. The 103(a) rejection when taken as a whole clearly demonstrates that Grilli et al. contemplates the prevention and treatment of glutamate receptor-mediated neuronal damage with NSAIDs, that Bakhshi teaches the applicant's claimed delivery method and that Myseros et al. demonstrates that glutamate

antagonism improves both mortality and morbidity in an animal model of traumatic brain injury. For these reasons and the reasons of record the examiner maintains the 103(a) rejections of the prior office action. The rejections are reproduced below.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 5-7, 29, 30, 32-36, 38-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grilli et al. (WO 98/20864) in view of Bakhshi et al. (*Journal of Neuro-Oncology*, 26, 133-9) and further in view of Myseros et al. (The rationale for glutamate antagonists in the treatment of traumatic brain injury, Ann NY Acad Sci, 1995, 765:262-271).

Grilli et al. teaches the treatment of Alzheimer's disease through the use of NSAIDs (Abstract). Sodium salicylate and salicylamide are specifically taught as NSAIDs useful in the invention disclosed therein (p 3). Neuronal damages (i.e.

neurotrauma or neuronal injury) related to Alzheimer's disease are specifically taught as treatable by the NSAIDs disclosed therein (p 6). Generally, cranial and spinal traumas are also taught to be treatable by the methods disclosed (p 6). Grilli et al. teach, on page 5, that non-steroidal anti-inflammatory drugs can be used in the prevention and/or treatment of glutamate receptor-mediated neuronal damages, independently of any anti-inflammatory properties. Further the NSAIDs show a protective activity against glutamate-induced neurotoxicity. Grilli et al. lacks a specific teaching of the claimed mode of administration and a specific teaching of the treatment of neurotrauma associated with traumatic brain injury (i.e., traumatic brain trauma and diffuse axonal injury associated with such).

Bakhshi et al. teaches the administration of CNS drugs via intrathecal catheter. Such administration is taught to alleviate adverse systemic effects, peripheral metabolism of centrally acting drugs, inadequate blood-brain barrier penetration, etc. See page 133. Administration of drugs effective for treating Alzheimer's disease is specifically taught as useful in this manner. See page 137.

Myseros et al. teach, on page 262, that excitotoxic damage to neurons and glia may develop as a consequence of excessive release of excitatory amino acids after primary impact injury, ischemic events, and hematoma. Further it appears that glutamate antagonists have potent neuroprotective effects for head-injured patients. On page 263, Myseros et al. teach that diffuse axonal injury is a process that does not occur instantaneously after a traumatic brain event, but rather that after impact an immediate and massive release of neurotransmitters (including glutamate) is noted and

structural axonal disruption occurs later. Myseros et al. teach, on page 264, that the structural axonal lesions seen after sheer injury may not be caused by a mechanical process, but by a failure of ionic homeostasis mediated via the glutamate channel. Further, on page 265, Myseros et al. teach that treatment of rats with a glutamate antagonist in the fluid percussion model (an animal model for traumatic brain impact and associated diffuse axonal injury) results in a dose-dependent improvement in both mortality and memory and motor tasks.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the composition of Grilli et al. for the treatment of Alzheimer's disease (and any neuronal damage associated therewith) and neurotrauma (specifically traumatic brain injury and associated diffuse axonal injury) because (1) Grilli et al. teaches the administration of the composition for said treatment generally (and that said compounds can be used in the prevention and/or treatment of glutamate receptor-mediated neuronal damages); (2) Bakhshi et al. teaches the administration of drugs to the CNS for the treatment of Alzheimer's Disease via intrathecal catheter and (3) Myseros et al. teach that prevention and/or treatment of glutamate neurotoxicity (specifically by glutamate antagonists) results in improvement in both mortality and morbidity of patients. One would have been motivated to administer the composition of Grilli et al. by intraventricular or intrathecal injection, facilitated by catheter, because of an expectation of success in treating neuronal damage associated with Alzheimer's, as taught by Grilli et al. and in treating neurotrauma as taught by Myseros et al.; an expectation of success in alleviating adverse systemic effects associated with the

administration of the drug, ensure adequate blood-brain barrier penetration, etc., as taught by Bakhshi et al.

It is noted that the recitation of the limitation of "non-inhibitory of platelets" is a recitation of a limitation as to the property of the drug. It is also noted that the recitation provides no information as to how it would limit the structure of the claimed NSAIDs. Accordingly, since Examiner has shown that it is known to administer the same compositions as instantly claimed, the compositions would obviously be non-inhibitory of platelets. A compound and its properties are inseparable. *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963).

Claims 4, 31, 37 and 41-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grilli et al. in view of Bakhshi et al. and Myseros et al. as applied to claims 1, 5-7, 29, 30, 32-36, 38-40 above, and further in view of McGeer et al. (USPN 5192753).

Grilli et al. in view of Bakhshi et al. and Myseros et al. apply as disclosed above. It is noted that Grilli et al. also teaches that salicylic acid, acetylsalicylic acid, salicylates, etc. and pharmaceutically acceptable salts of acetylsalicylic acid are useful as NSAIDs in the treatments disclosed therein (p 3). The references lack a teaching of choline magnesium trisalicylate.

McGeer et al. teaches arylcarboxylic acids such as salicylic acid, acetylsalicylic acid, choline magnesium trisalicylate, salicylate, etc. as NSAIDs useful for the treatment of Alzheimer's disease (col. 1, lines 36-65).

It would have been obvious to one of ordinary skill in the art to utilize the specific NSAID choline magnesium trisalicylate in a method of Grilli et al. and Bakhshi et al. because (1) Grilli et al. teaches the use of derivatives of acetylsalicylic acid as NSAIDs useful for the treatment of neuronal damage associated with Alzheimer's disease; (2) Grilli et al. teaches that salicylates and pharmaceutical acceptable salts thereof are useful as NSAIDs in the treatment of neuronal damage associated with Alzheimer's disease; and (3) McGeer et al. teaches that choline magnesium trisalicylate is a salicylate suitable for the treatment of Alzheimer's disease. One would have been motivated to utilize the specific salicylate choline magnesium trisalicylate because of the expectation of success in treating neuronal damage associated with Alzheimer's disease by administering a derivative of acetylsalicylic acid to a patient in need thereof, as taught by Grilli et al.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leonard M. Williams whose telephone number is 571-272-0685. The examiner can normally be reached on MF 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LMW

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER